

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-512**

SUMMARY REVIEW

Deputy Office Director Decisional Memo

Date	10/19/2010
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA#	22-512
Applicant Name	Boehringer-Ingelheim GmbH
Date of Submission	4/19/2010
PDUFA Goal Date	10/19/2010
Proprietary Name / Established (USAN) Name	Pradaxa Dabigatran etexilate
Dosage Forms / Strength	Oral capsules: 150 mg and 110 mg
Approved Indication	...for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Action:	<i>Approval of 150 mg strength; non-approval of 110 mg strength</i>

Material Reviewed/Consulted Action Package, including:	
Project Manager	Alison Blaus
Medical Officer Safety Review	Nhi Beasley
Medical Officer Efficacy Review	Aliza Thompson
Pharmacometric review	Kevin Krudys
Statistical Review	Steven Bai
Pharmacology Toxicology	Patrician P. Harlow, Albert DeFelice, Paul C. Brown
Chemistry Manufacturing and Controls	Charles Jewell and Prafull Shiromani
Statistical Review and Evaluation of Carcinogenicity Study	Steve Thomson
Biopharmaceutics	Tapash K. Ghosh
Clinical Pharmacology	Elena V. Mishina, Peter Hinderling, Sudharshan Hariharan, Michael Pacanowski
Environmental Assessment	Raanan A. Bloom
Division of Scientific Investigations	Arindam Dasgupta, Sharon Gershon, Tejashri Purohit-Sheth
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Judy Park, Cathy A. Miller
Division of Risk Management, Office of Surveillance and Epidemiology	Cynthia LaCivita, Sharon Mills, Shawna Hutchins
Division of Drug Marketing, Advertising and Communications (DDMAC)	Emily Baker, Zarna Patel, Iris Masucci
Hepatic Effects, Office of Surveillance and Epidemiology	John R. Senior
Cross-Discipline Team Leader	Abraham Karkowsky
Proprietary Name Review	Judy Park, Cathy A. Miller
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge

Action:

The Division of Cardiovascular and Renal Products is recommending approval of dabigatran etexilate, 150 mg capsules for oral administration, for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). I concur with their recommendation for approval. The applicant also sought approval of a 110 mg strength capsule; however, the Division came to a virtually unanimous conclusion that the 110 mg capsule should not receive marketing approval at this time, and I agree with that course of action.

Introduction:

Dabigatran etexilate is a synthetic small molecule pro-drug for dabigatran, a competitive, reversible, direct thrombin inhibitor, and a representative of a new therapeutic class of direct thrombin inhibitors. Because thrombin participates in a number of critical functions in the clotting cascade, including the conversion of fibrinogen to fibrin, inhibitors of thrombin are anticoagulants. The proposed use is for the prevention of stroke and systemic emboli in patients with non-valvular AF. Currently, warfarin is used for this indication, although low-risk patients may be managed with aspirin.

Dabigatran etexilate was approved in Europe in March, 2008, for *short-term use* for primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery. Two strengths are marketed: 110-mg and 75-mg capsules. The recommended dose is 220 mg QD (two 110-mg capsules). For patients with moderate renal impairment or age > 75 years, the recommended dose is 150 mg QD (two 75-mg capsules).

Prior investigational experience with ximelagatran, a direct thrombin inhibitor of the same class, is relevant to the dabigatran NDA: 1) With respect to the demonstration of efficacy, an open-label clinical trial of ximelagatran versus warfarin for the prevention of strokes in patients with AF (SPORTIF III) showed a numerical trend towards efficacy, whereas a subsequent double-blind trial (SPORTIF V) showed the *opposite*. This experience suggests that biases inherent in an open-label trial could provide misleading findings in this patient population; 2) Ximelagatran appeared to be hepatotoxic. Thus, monitoring in the dabigatran development program was comprehensive: designed to detect abnormalities in hepatic markers at an early stage when toxicity would be reversible.

Note: Throughout this memorandum, the to-be-marketed pro-drug, dabigatran etexilate mesylate, will be referred to simply as “dabigatran.”

Regulatory Background:

The IND for dabigatran for this indication was filed on 7/7/2003. The applicant met with the Division for an End of Phase 2 meeting on 3/24/2005. The protocol for a single pivotal phase 3 trial (RE-LY) was submitted for Special Protocol Assessment, and the Division provided comments on 7/11/2005.

A summary of RE-LY was presented to the Division on 8/17/2009 and the results were published on 9/17/2009 (*New Engl J Med*, 2009; 361:1139-51).

A rolling review was granted for this NDA, with the final “piece” of the submission arriving 12/15/2009.

The Division refused to file the application because of questions regarding data accuracy. In short, the clinical reviewers quickly and fairly easily identified a number of errors in the transfusion dataset, a dataset bearing importantly on planned safety analyses on bleeding, as well as transposition errors in another dataset. The Division and the applicant met 2/18/2010 to discuss the issues, and reached an acceptable plan for resolving the Division's concerns. Following resolution of the data accuracy issues, the NDA was re-submitted on 4/19/2010, and filed.

Chemistry Manufacturing and Controls (CMC):

Pursuant to their initial review, the CMC team provided a number of questions that were communicated to the applicant in an information request (IR) letter, dated 6/29/2010, and the applicant's responses were deemed adequate. In addition, the ONDQA Biopharm and Environmental Assessment reviews found no pending issues. Accordingly, the NDA was recommended for approval from a CMC perspective.

Pharmacology/Toxicology:

The review found the application approvable, with most of the toxicities observed in the non-clinical studies attributable to the pharmacodynamic effects of either dabigatran or the pro-drug, dabigatran etexilate. For other toxicities, satisfactory safety margins were demonstrated.

Female Han Wistar rats received dabigatran etexilate at doses of 0, 15, 70, and 200 mg/kg from gestation Day 7 to 16 (post organogenesis), and were killed on Day 22. At the high dose, resorption of fetuses was significantly increased, and there was a decrease in the number of viable fetuses, although there were signs of extreme maternal toxicity that obfuscated interpretation of the findings. Although the increase in resorption at the mid-dose was not statistically significant, the resorption rate in dabigatran-treated animals fell outside of historical control values and was therefore of some concern. Likewise, in the pre- and post-natal development studies, some dams died perinatally, the birth index decreased, and post-implantation loss increased in a dose-related manner, beginning at 70 mg/kg (treatment administered from gestation Day 7 to weaning).

In labeling, the pharmacology/toxicology review team requested a more explicit warning to women of child-bearing potential of dabigatran's embryo/fetal and perinatal toxicity to offspring. Whereas the applicant proposed labeling stating that dabigatran decreases implantations in rats, the review team requested that the label also note that dabigatran increases the number of dead offspring, and, in rats, increases the incidence of fetal skeletal variations related to delayed or irregular ossification of skull bones and vertebrae. In the labor and delivery section of the label, they wished to note that dabigatran led to the deaths of some rats. These suggestions have largely been incorporated into labeling.

Dr. Karkowsky suggested in his review that "Despite the temptation to employ dabigatran, a convenient oral anti-coagulant, for the treatment of pregnant women with DVTs, the off-label use of DE in this population should be discouraged." Pregnant females with prosthetic heart valves represent another population for which there will be temptation to use dabigatran off-label. The mainstay of anticoagulant treatment for patients with prosthetic valves is warfarin, but women are generally switched to heparin (or low molecular weight heparin) during pregnancy (warfarin is pregnancy category X). Obviously, there may be temptation to use off-label dabigatran in this small, albeit important, population, despite concerns in labeling.

Relevant to gastrointestinal adverse reactions observed in the pivotal clinical trial, RE-LY, gastric secretion and gastrointestinal transit were not significantly affected by either oral dabigatran etexilate mesylate or intravenous dabigatran in non-clinical studies, except that modest decreases in gastric emptying were observed with both intravenous and oral administration of dabigatran and dabigatran etexilate mesylate, respectively.

Carcinogenicity:

Two-year carcinogenicity studies were carried out in mice and rats. Although increased incidence of some tumor types was observed in both species, the frequencies were within the historical range, and the p-values did not reach the statistical thresholds necessary to characterize the findings as drug-related.

Neither dabigatran etexilate nor the active drug was genotoxic in the usual bacterial strains or in mammalian cells. Neither dabigatran etexilate nor the active drug induced excessive micronucleus formation. None of the nine impurities specified by the CMC review were positive in genotoxicity assays.

Site Inspections:

Two inspected sites were found to have deviations commensurate with the issuance of FDA-483 forms, but the deviations were not considered to have the potential to affect the results of the trial.

Pharmacokinetics:

Dabigatran is not absorbed orally; however, the etexilate pro-drug is orally bioavailable. Dabigatran etexilate is manufactured as a salt as dabigatran etexilate mesylate, which itself possesses no anticoagulant activity.

Bioavailability is low, i.e., approximately 3 to 7%. Following oral administration, dabigatran etexilate is hydrolyzed to dabigatran by hepatic esterases, and conjugated with glucuronic acid to form acyl glucuronides. The latter are said to retain some pharmacologic activity. Peak plasma concentrations are observed approximately 2 hours after oral administration in the fasting state, and are delayed by 2 hours when the drug is administered with a high-fat meal. Overall exposure is unchanged by meals; therefore, dabigatran may be administered without regard to food.

Dabigatran is mainly (80-85%) eliminated in the unchanged form via glomerular filtration, thus renal function is the main determinant of exposure. Approximately 20% of dabigatran is excreted as glucuronides.

Other key findings summarized in the clinical pharmacology review:

- pharmacokinetics are dose-proportional after single oral doses from 10 to 400 mg
- half-life is 12-17 hours
- volume of distribution is 50-70L
- protein binding is approximately 35%
- accumulation is 1.6 to 2.3 for both AUC and C_{max}

- dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes.

The prodrug dabigatran etexilate, but not the active moiety dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). In phase I studies, P-gp inhibitors such as verapamil and ketoconazole increased dabigatran plasma concentrations by about 1.5- and 2.5-fold, respectively. Conversely, in RE-LY, P-gp inhibitors only modestly increased the mean plasma concentrations of dabigatran and had little or no effect on bleeding. Whereas the phase I studies were designed to estimate maximum potential drug-drug interactions by controlling the timing of drug administration, the timing of administration of concomitant drugs with respect to dabigatran was random in RE-LY. Presumably, this accounts for at least some of the difference.

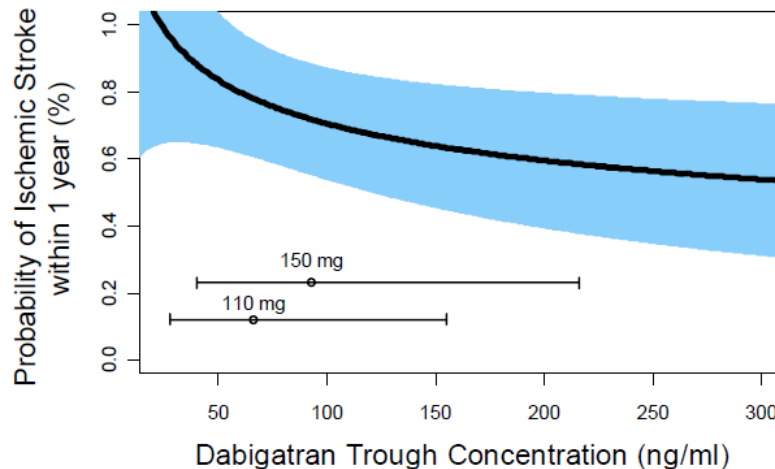
Importantly, the clinical pharmacology reviewers interpreted the RE-LY findings as suggesting that dabigatran doses higher than 150 mg bid may provide additional reduction of stroke, with an acceptable increase in bleeding risk. They pointed to the significant dose-dependent decrease in ischemic strokes from 110 mg bid to 150 mg bid (1.3% to 0.9% per year, respectively), indicating potential for further improvement in efficacy. They acknowledge that higher doses would likely lead to an increased risk of bleeding. But they note, interestingly, that the 2-fold increase in dabigatran exposure in patients with moderate renal impairment was associated with a more favorable hazard ratio (HR) for stroke. They noted that advancing renal impairment was not associated with higher rates of bleeding. I disagree somewhat with the latter statement, and would say that the HR for major bleeding (relative to warfarin) does become less favorable as renal function worsens, but the HR is never less favorable than unity (see medical officers' review, figures 15 and 16; the HRs for dabigatran 150 bid versus warfarin are 0.84, 0.89, and 0.94 in patients with estimated creatinine clearance (CrCL) ≥ 80 , 50 to 80, and 30 to 50 mL/min, respectively).

They concluded, therefore, that there would be value in evaluating the risk-benefit profile of dabigatran doses in excess of 150 mg bid post-approval, for example, 300 mg BID. Considerations regarding doses higher than 150 mg bid will be discussed later in this memorandum under "Adequacy of Dose Exploration."

The FDA pharmacometrics reviewers modeled the relationship between dabigatran concentration and the yearly probability of ischemic stroke in RE-LY. The model considered the following risk factors: age, sex, weight, history of stroke or transient ischemic attack (TIA), diabetes mellitus and age ≥ 65 years, coronary artery disease and age ≥ 65 years, hypertension and age ≥ 65 years, and aspirin use. The analysis included only subjects in whom there were both trough dabigatran concentrations and full data on covariates (approximately 77% of enrolled subjects).

The results are shown below. The blue shaded region represents the 95% CI of the probability of stroke, and the error bars represent the 10th to 90th percentiles of the dabigatran trough concentrations. As expected given the closeness of the 110 and 150 mg doses, there is substantial overlap between the trough concentrations produced by the two regimens. The analysis identified age, weight, history of stroke/TIA, diabetes mellitus and age ≥ 65 years, and trough dabigatran concentration as significant risk factors. Of note, the parameter describing the relationship between dabigatran concentration and stroke was only marginally statistically significant ($p=0.056$).

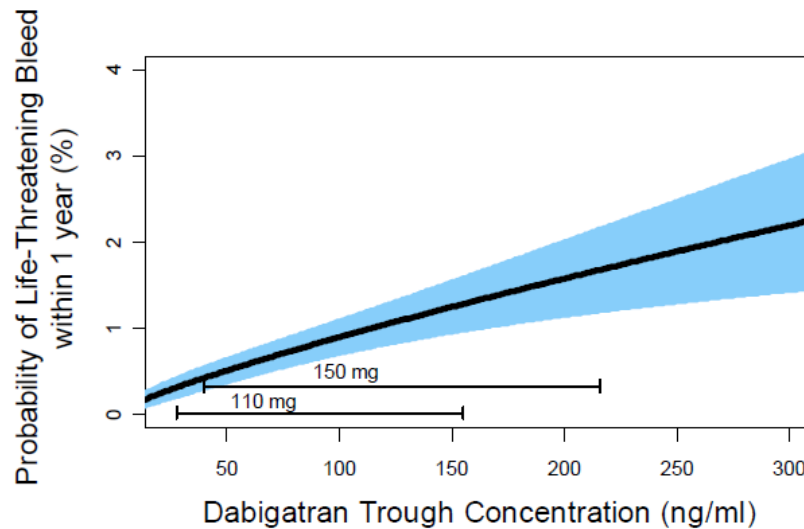
For the 110 mg bid and 150 mg bid doses, the predicted probabilities of a stroke in one year were 0.79% and 0.72%, respectively, based on the point estimates. The difference between these estimates, 0.07%, represents 0.7 strokes per 1000 patient-years.



The J-shaped curve shows a rapid decrease in probability of stroke from a concentration of zero through approximately 70 ng/mL, with only gradual a reduction in risk at higher concentrations. Dr. Karkowsky suggested that the difference between the two dabigatran doses in prevention of stroke could be a function of the population of subjects in the 110 mg bid dose group with trough concentrations below 70 ng/mL.

The pharmacometrics reviewers also modeled the relationship between dabigatran concentration and time to life-threatening bleed in RE-LY. They analyzed all dabigatran-treated subjects for whom there were trough dabigatran measurements and complete information on covariates and life-threatening bleeds (approximately 70% of dabigatran-treated subjects). They explored the same risk factors used for the stroke analysis.

The predicted probability of a life-threatening bleed vs. dabigatran trough concentration is shown below. The relationship is fairly linear. For the 110 and 150 mg bid regimens, the predicted probabilities of a life-threatening bleed in one year are 0.62 and 0.83%, respectively, based on the point estimates, with the difference representing 2.1 life-threatening bleeding events per 1000 patient-years.



Evidence of Effectiveness:

The RE-LY trial provides evidence of effectiveness for dabigatran for the indication sought by the applicant: prevention of strokes and systemic emboli in patients with non-valvular AF. Subjects were randomized 1:1:1 to dabigatran 150 mg BID, dabigatran 110 mg BID, or warfarin. The trial employed an unusual “hybrid” design: treatment assignment to either dabigatran or warfarin was open-label, whereas treatment assignment to the two dabigatran doses was double-blind. The design permitted comparison of the two dabigatran groups for efficacy and safety without the bias inherent in an open-label study.

Enrolled subjects had non-valvular AF and at least one additional risk factor: previous ischemic stroke, systemic embolism, or TIA; heart failure; age >75 years; or age >65 with diabetes mellitus, coronary artery disease, or hypertension. Major exclusion criteria included hemodynamically significant valvular disease, prosthetic valve, recent stroke, high risk of bleeding, liver disease, and anemia.

The primary endpoint of the study was time to first occurrence of stroke (both ischemic and hemorrhagic) or systemic embolism.

There were two 2° endpoints:

- stroke, systemic embolism, and all-cause death
- stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular death (including bleeding deaths).

Because there was no prospective plan to control Type-I error for the 2° endpoints, however, they should be considered largely exploratory.

The trial included numerous exploratory endpoints, also without a rigorous statistical plan to control Type-I error.

The primary hypothesis was that dabigatran at either dose was non-inferior to warfarin in preventing stroke and systemic embolism. A non-inferiority margin of 1.46 was proposed by the applicant, based on historical placebo-controlled trials and the 95% rule. M1 was calculated as the lower bound of the 95% confidence interval (CI) of the HR of warfarin versus placebo, as derived from 6 trials carried out from 1989 to 1992. The goal was to demonstrate preservation of at least 50% of warfarin's effect size, where a statistical "win" would rule out this non-inferiority margin, M2 (based on the 95% CI). The applicant used the linear risk ratio scale in their calculations, which provided a value of 1.46 for M2. FDA made clear its preference for use of a log scale, however, for which the calculated non-inferiority margin was 1.38. (In spite of this disagreement, both dabigatran doses were non-inferior to warfarin, even using the more stringent FDA-recommended margin, so the disagreement is a moot point.)

The Hochberg procedure was used to control alpha for the two comparisons of dabigatran to warfarin.

One important study amendment (#1) was designed to assure that 50% of the enrolled subjects would be vitamin K antagonist (VKA)-naïve. Warfarin tends to be less safe and effective when therapy is first initiated, relative to when the drug has been used chronically and the International Normalized Ratio [INR] is well-controlled. Thus, assuring that the trial would enroll adequate VKA-naïve subjects was a reasonable consideration for RE-LY.

The study enrolled 18,113 subjects, or approximately 6000 subjects per treatment group. As expected in a trial of this size, baseline factors were well-matched between groups. The demographics and disease-specific characteristics appear consistent with the to-be-indicated AF population. Mean age was 71; 63% of subjects were male. Subjects were characterized fairly evenly as paroxysmal, permanent, and persistent AF (approximately one-third each). Half the subjects were VKA-naïve (by design, see above). The CHAD2 score was fairly evenly divided between 1, 2, and 3, with 2-3% CHAD2 score 0.

Approximately 36% of the subjects were enrolled at US or Canadian sites.

Some 96% of the subjects completed the study in all treatment groups, but there were more discontinuations in the dabigatran groups. Specifically, for subjects who received at least 1 dose of study drug, 15% of subjects in the warfarin group discontinued, whereas 19 and 20% of subjects in the dabigatran 110 mg and 150 mg groups discontinued, respectively.

The numbers of strokes and systemic emboli (SEE) their yearly event rates (in parentheses) are shown below (medical officers' review, Table 30):

	Dabigatran 110 N (%)	Dabigatran 150 N (%)	Warfarin N (%)
Subject years of follow up	11899	12033	11794
Subjects with stroke/SEE	183 (1.5)	134 (1.1)	202 (1.7)
Subjects with stroke*	171 (1.4)	122 (1.0)	186 (1.6)
Ischemic	152 (1.3)	103 (0.9)	134 (1.1)
Hemorrhagic	14 (0.1)	12 (0.1)	45 (0.4)
SEE	15 (0.1)	13 (0.1)	21 (0.2)

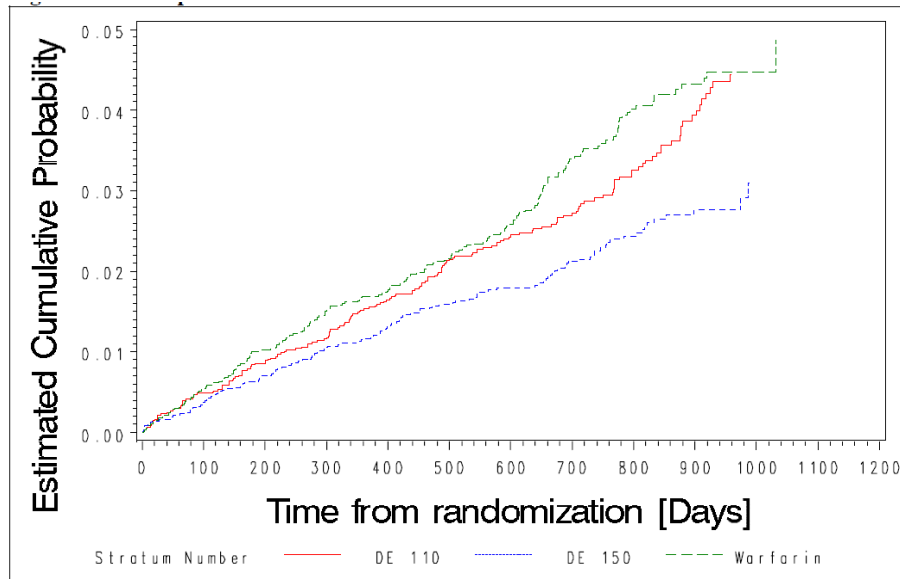
*The numbers of ischemic and hemorrhagic strokes do not sum to the total number of strokes because some strokes received “uncertain classification.”

Hazard ratios for the components of 1° endpoint are shown below (medical officers’ review, Table 31):

	Dabigatran 110 vs. warfarin		Dabigatran 150 vs. warfarin	
	HR (95% CI)	p-value superiority	HR (95% CI)	p-value superiority
Stroke	0.91 (0.74, 1.12)	0.38	0.64 (0.51,0.81)	.0001
Ischemic	1.13 (0.89,1.42)	0.31	0.75 (0.58,0.97)	0.030
Hemorrhagic	0.31 (0.17,0.56)	0.0001	0.26 (0.14,0.49)	<0.0001
SEE	0.71 (0.37,1.38)	0.31	0.61 (0.30,1.21)	0.16

For the primary endpoint, both doses of dabigatran satisfy FDA’s more conservative non-inferiority margin of 1.38. For the primary endpoint the dabigatran 150 mg bid dose was superior to warfarin. There are reasons, however, why a superiority claim for dabigatran 150 mg bid is not warranted (see below, “Superiority to Warfarin”).

The Kaplan-Meier estimate of time to first stroke/systemic embolism is shown below (statistical review, figure 3.1):



The results on the 1° efficacy endpoint are robust to sensitivity analyses, and consistent across numerous subgroups, including demographic factors, CHADS2 score, history of prior stroke,

concomitant cardiovascular diseases, CrCL, type of AF, and VKA use at entry. There is no important difference between results of the on-treatment and as-randomized analyses. The findings in North America were largely consistent with the study results as a whole. The reduction in strokes (dabigatran 150 bid vs. warfarin) was apparent at all severities of stroke, i.e., across most Rankin scores. Based on the statisticians' analysis on the impact of different end-of-trial dates, both dabigatran doses achieved non-inferiority long before end-of-trial, and the 150 mg bid dose achieved superiority to warfarin more than one year before end-of-trial.

The all-cause mortality results in RE-LY are of some interest, and will be summarized briefly. Annualized all-cause mortality rates were 3.8, 3.6, and 4.1% in the dabigatran 110 bid, dabigatran 150 bid, and warfarin groups, respectively. There were questions regarding the inclusion and exclusion of certain deaths, but the most favorable analysis provided a HR of 0.88 for the comparison between dabigatran 150 bid and warfarin, with 95% CI 0.77 to 1.00, $p=0.052$. Even if the result had been statistically significant, it was not corrected for multiplicity. Moreover, a key consideration in gauging the efficacy of warfarin is INR control. The clinical reviewers considered all-cause mortality at centers where the time in therapeutic range (TTR) in warfarin-treated subjects was "better" and "worse," dichotomized by the median TTR (67%), an analysis that preserves the randomization. Virtually all of the reduction in death was attributable to centers where INR control was worse than the median. Thus, even if dabigatran 150 mg bid had been statistically significantly superior to warfarin after correction for multiplicity, we would have been reluctant to declare superiority because the efficacy of warfarin appears to be dependent on how it is used.

Safety:

The primary safety issue for dabigatran is related to its pharmacodynamic effect, i.e., bleeding.

Bleeding:

Bleeding events were categorized as major or minor. Major bleeds were defined as bleeding associated with a decrease of hemoglobin of 2 g/dL or the need for transfusion of two units of blood, or symptomatic bleeds into a critical area. Major bleeds were further categorized as life-threatening bleeds if they were: fatal; symptomatic intracranial; or provoked a reduction of hemoglobin of 5 g/dL with hypotension requiring intravenous inotropic support or surgical intervention. Major bleeding events were adjudicated.

Major bleeding events are summarized here, from Table 58 of the medical officers' review:

	dabigatran 110 mg bid	dabigatran 150 mg bid	warfarin
N=	6015	6076	6022
Subjects with major bleed (%)	342 (5.7%)	399 (6.6%)	421 (7.0%)
Total number of major bleeds	406	489	483
Life-threatening bleeds (%)	159 (2.6%)	193 (3.2%)	233 (3.9%)

There were substantially fewer events in the dabigatran 110 bid group compared with either dabigatran 150 mg bid or warfarin. There was no significant difference in bleeding events between the dabigatran 150 bid group and the warfarin group.

Of note, the risk of bleeding was dependent on the level of INR control. Warfarin-treated subjects with better control of INR, estimated as TTR, fared about the same as subjects who received dabigatran with respect to major bleeding events. Dabigatran's advantage on bleeding, relative to warfarin, was in subjects at centers where mean TTR was worse than the median.

Hazard rates of major bleeds based on center level INR control (TTR) for the RE-LY study, from medical officers' Table 50:

TTR center level INR control		Worst quartile TTR <58.5%	Second quartile TTR ≥58.5% to <66.8%	Third quartile TTR ≥66.8% to < 74.2%	Best quartile TTR ≥74.2%
Dabigatran 110 bid vs. warfarin	HR	0.64	0.74	0.90	0.93
	95%CI	0.46, 0.88	0.57, 0.97	0.69, 1.17	0.68, 1.26
	p-value	0.005	0.03	0.43	0.62
Dabigatran 150 bid vs. warfarin	HR	0.68	0.90	1.00	1.2
	95%CI	0.50, 0.93	0.70, 1.16	0.77, 1.30	0.90, 1.60
	p-value	0.02	0.41	1.00	0.21

Gastrointestinal Adverse Reactions:

There were excess gastrointestinal (GI) adverse reactions in the dabigatran groups. Dyspepsia-like symptoms (dyspepsia, upper abdominal pain, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in approximately 12.5% of subjects who received either dose of dabigatran, vs. 5.9% in warfarin. Gastritis-like symptoms, including gastritis, gastroesophageal reflux disease, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, and erosive hemorrhagic gastritis, occurred in 5.0, 4.2, and 2.4% of subjects in the dabigatran 110, dabigatran 150, and warfarin groups, respectively. Dyspepsia was responsible for 1% of the discontinuations in dabigatran-treated subject, versus 0% in warfarin. The time course of these reactions, and, once they occurred, their likelihood of abating, were not well-described. It is fair to say, however, that the reactions did not exhibit a dose-response.

Of note, dabigatran is not well-absorbed, and one could posit a local GI effect, but this is purely speculative. Gastrointestinal bleeding occurred more frequently with dabigatran than warfarin, but the bleeding location was not predominantly in the upper GI tract.

In the non-clinical studies, neither gastric secretion nor gastrointestinal transit was significantly affected by dabigatran, although there was a modest decrease in gastric emptying.

Considering all of the data, the mechanism accounting for the GI adverse reactions remains unclear, but the risk will be described in labeling.

Myocardial Infarction:

In RE-LY, the rate of myocardial infarction (MI) was higher in dabigatran-treated subjects than in warfarin-treated subjects. The rates were essentially the same in both dabigatran groups (i.e., no dose-response). As described in the medical officers' review, the reason(s) for the higher rate of MI with dabigatran are unclear. Baseline subject characteristics and medication use

were similar between treatment arms and do not appear to explain the finding. The imbalance in MIs was seen on-drug as well as off-drug. The higher rate of MI with dabigatran may represent an adverse effect of dabigatran, a beneficial effect of warfarin, or play of chance. The description of frequencies of MIs will be included in labeling without explanation.

Hepatic Effects:

Dabigatran is structurally similar to ximelagatran, a member of the same class of thrombin inhibitors. Because of previous hepatotoxicity attributed to ximelagatran, the Division consulted Dr. John Senior, Office of Surveillance and Epidemiology, to assess the hepatic effects of dabigatran in RE-LY. In the controlled trials of ximelagatran, there was an increased incidence of elevated serum aminotransferases compared with warfarin, and also concern about potential "Hy's Law" cases.

In RE-LY, there were 11 and 13 potential Hy's Law cases in the dabigatran 110 and 150 mg groups, respectively, and 20 potential cases in the warfarin group. The large number of potential Hy's Law cases in the warfarin group was unexpected, given that warfarin is not known to cause hepatotoxicity.

Two expert hepatologists, (b) (4) and John Senior, independently reviewed the clinical data for each case, and found no potential Hy's Law cases for any of the drugs, and found no indication of a greater frequency or severity of liver injury with dabigatran than warfarin.

In a subsequent review, they evaluated 4 post-marketing cases reported from countries where dabigatran has been approved for prevention of thromboembolism following orthopedic surgery. Unfortunately, the reported cases lacked sufficient detail to permit an adequate review.

Their conclusions and recommendations are as follows:

1. The findings from these cases do not suggest that dabigatran is likely to cause serious liver injury, but they do not rule it out. Dabigatran should not be assumed to be completely safe from causing idiosyncratic liver toxicity; some cases may occur if large numbers of patients are treated over the long term.
2. Routine monitoring of liver enzymes has been found to be inefficient, ineffective, and burdensome, and is not recommended.
3. Because the atrial fibrillation population tends to be elderly with a high prevalence of cardiac disorders and other problems likely to cause liver dysfunction, it would be advisable for patients to have pre-treatment evaluation of liver disease.

Important Issues:

Study Design:

The review team and the Advisory Committee paid much attention to the "hybrid" study design, in particular that fact that randomization to warfarin or dabigatran was open-label. If we were now reviewing only a single open-label study comparing one dose of dabigatran to warfarin, interpretation could be difficult. We would worry about biases affecting both ascertainment of events and patient management. We would be concerned about the adequacy of INR control relative to the studies used to establish the non-inferiority margin. We would remind ourselves of the inconsistency between the double-blind and open-label trials in the clinical development of ximelagatran.

However, because RE-LY incorporated a randomized double-blind comparison of the lower and higher doses of dabigatran, we can have greater confidence in the results. Although the comparison of dabigatran 150 mg bid to 110 mg bid was a post-hoc analysis, the results show a statistically compelling difference on the 1^o endpoint of stroke or systemic emboli (1.1 vs. 1.5 events per 100 patient-years, for the higher and lower doses, respectively, HR = 0.72, 95% CI 0.58 to 0.90; $p = 0.004$).

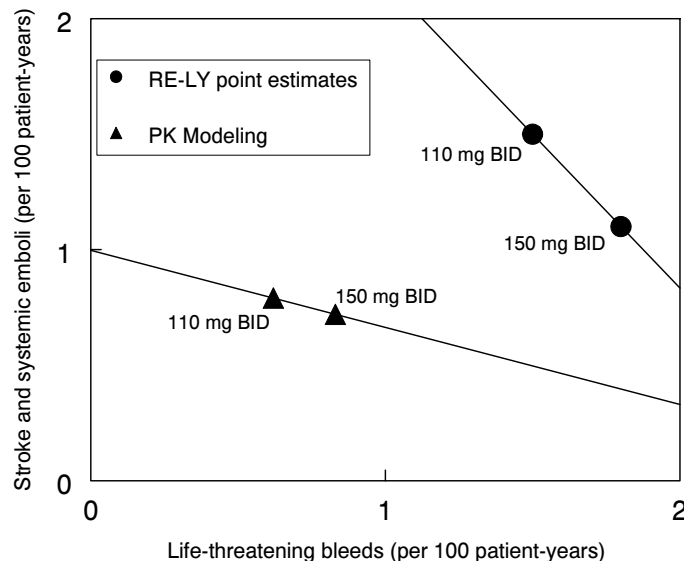
Adequacy of Dose Exploration:

Some have voiced concern that a dose higher than 150 mg bid should have been studied, based on the prediction that a higher dose would cause a further reduction in stroke with an acceptable increase in bleeding. This question of adequacy of dose exploration was posed to the Advisory Committee, who by and large expressed the view that dose exploration was adequate.

In my view, much of the confusion comes down to whether one bases their projections on the actual RE-LY results or on the pharmacologic modeling. The figure below shows risk-benefit assessments for the two doses of dabigatran using two different methods. One analysis (solid circles) bases the risk-benefit on the point estimates of annualized rates of stroke/systemic embolism rates and life-threatening bleeds from RE-LY; the other (triangles) bases the risk-benefit on the point estimates of annualized stroke rates and life-threatening bleeds from the modeling.

Considering the point estimates of results of RE-LY, the slope of - 4/3 corresponds to 4 strokes prevented at a cost of 3 life-threatening bleeds.

For the PK modeling analysis, the slope of - 1/3 corresponds to 1 stroke prevented at a cost of 3 life-threatening bleeds.



Given that the plot is based on point estimates that do not take uncertainty into consideration, the results may not be mutually exclusive – but they are nevertheless difficult to reconcile! They could lead one to arrive at very different conclusions regarding the advisability of studying a dose in excess of 150 mg bid. Few would argue about preventing 4 strokes at a cost of 3 life-threatening bleeds, but some might argue that prevention of 1 stroke at a cost of 3 life-threatening bleeds is a bad trade. Clearly, this issue may warrant worth some additional thought in terms of the advisability of future studies.

Two doses or one?:

Dabigatran at a dose of 150-mg bid was superior to warfarin on the primary endpoint, and similar on bleeding. The 110-mg bid regimen was non-inferior to warfarin on efficacy, and caused less bleeding. Why shouldn't patients and practitioners have a choice?

It is clear that the higher dose is what the vast majority of patients, if not all patients, should receive. There were numerically more ischemic strokes in the dabigatran 110 bid group (152, 1.3% per year) than the warfarin group (134, 1.1% per year). Moreover, if we accept the validity of the post-hoc analysis showing that the 150-mg dose is statistically superior to the 110-mg dose in preventing stroke, it could be argued that it wouldn't even be *ethical* to use the lower dose. The sponsor tried, and the review team tried, to identify a population for whom the 110-mg dose would be appropriate. There was considerable focus on the very elderly population; the data in favor of a 110-mg dose were suggestive, but not entirely convincing.

Dr. Thompson also considered the hypothesis that patients who experienced a major bleeding event on the higher dose might incur a reduced risk of bleeding if transitioned to the lower dose. Across all 3 treatment groups in RE-LY, she found that approximately 57% of subjects who experienced a major bleed either resumed study medication or had no interruption. Of these subjects, the percentages of subjects experiencing an *additional* major bleed were similar in the three treatment groups: 16%, 14%, and 12% for the dabigatran 110 mg, 150 mg, and warfarin groups, respectively. Thus, in this exploratory analysis, subjects who experienced a major bleed and subsequently received the higher dose of dabigatran were at no greater risk of experiencing a subsequent major bleed than those who received the lower dose. However logical it may seem, these findings do not support the concept that having the 110-mg strength capsule available for patients who experience a major bleeding event on the 150-mg strength capsule would be a useful strategy.

We know that warfarin is severely underutilized in the AF patient population, at a cost of increased strokes and disability. Some part of the resistance is fear of bleeding; the other part is related to fluctuations in INR, importance of diet, and the need for monitoring.

It is possible that patients who avoid warfarin because of the need for monitoring would consider dabigatran, irrespective of the dose or doses approved. It is also possible that some fraction of patients who avoid warfarin for fear of bleeding would find a 110-mg dabigatran regimen attractive, because it causes less bleeding. If some fraction of these patients, now under-treated, would take the lower dose of dabigatran, it argues for approval of the lower dose.

The other side of the coin is that approval of the 110-mg strength would provide the average patient with the option of taking a dose with less efficacy, leading to additional strokes and disability. One could attempt to discourage this behavior through education, but that strategy may not prove very effective. Many physicians tend to “play it safe” with anticoagulants and anti-platelet agents. The physician knows only who they hurt (patients with bleeding events);

they do not know who they help (they do not know whether a stroke is ever prevented in an individual patient). Because of this philosophy, there is a danger that the 110-mg dose would be over utilized, if approved.

For those who would like to see the 110-mg strength marketed, I am sympathetic. It is easy to envision some patients who would be excellent candidates for the 110-mg strength, i.e., patients with a history of GI bleeding, patients who are physically unstable and prone to falling, etc.

The Advisory Committee considered this issue at some length, and was split fairly evenly. The Division was unanimous in its opinion that only the 150-mg strength should be marketed, and Dr. Stockbridge was adamant about it.

My decision to approve only the 150-mg strength was a difficult one, based largely on the views of the Division, and my concern about loss of efficacy in many thousands of patients who would inappropriately opt for the lower dose, if available. If the applicant can make a stronger case for availability of the 110-mg strength, the Division can reconsider approval of the lower dose in a supplement.

Superiority to Warfarin:

Despite the apparent overall superiority of dabigatran to warfarin at the 150 mg BID dose in the population as a whole, the effect was driven entirely by patients in the warfarin group who were not as well controlled with respect to INR. Patients whose INRs were well-controlled with warfarin had the equivalent risk of having a stroke or fatal event as those treated with dabigatran 150 mg. Thus, the superiority is really conditional, and depends on how well warfarin is used. For “real world” warfarin use in a large population, dabigatran may be superior, but this may not be true for an individual patient. It is important, therefore, not to provide dabigatran with a superiority claim to warfarin, because it would imply that even those well-treated with warfarin should be switched to dabigatran. Clearly, that is not the case.

Non-valvular Atrial Fibrillation:

RE-LY was designed explicitly to study patients with non-valvular AF, and the enrollment criteria excluded patients with significant valvular disease. The indication will be restricted to patients with non-valvular atrial fibrillation. We recognize the potential for use in patients with significant native valvular disease, but such use would be off-label.

Renal Insufficiency:

In not approving the 110-mg strength, dosing options were limited for patients with severe renal insufficiency, but the Division concluded that it would be desirable to provide access to dabigatran for this patient population. Based on pharmacokinetic modeling, comparing pharmacokinetic data from RE-LY with data from a small study of subjects with compromised renal function, a dosing regimen of 75 mg bid appears appropriate for patients with estimated CrCL 15 to 30 mL/min. The 75-mg strength is already manufactured by the applicant (and marketed in the EU), and can be marketed in the US. Patients with CrCL \geq 31 mL/min should receive 150 mg bid. Based on data from 1 subject who received hemodialysis, dabigatran appears dialyzable, but there are not sufficient data to make any dosing recommendation in the dialysis population.

Risk Evaluation and Mitigation Strategy (REMS):

Section 505-1 of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1[a]). As noted above, there is concern regarding bleeding.

The review team has opined that a Medication Guide is required for dabigatran, because dabigatran poses a serious and significant public health concern. The Medication Guide is necessary because: 1) patient labeling could help prevent serious adverse effects; and 2) there are serious risks that patients should be made aware of, because information concerning the risks could affect patients' decisions to use, or continue to use dabigatran.

The review team, including staff from OSE, agrees that the elements of the REMS will be a Medication Guide and a timetable for the submission of assessments of the REMS.

Postmarketing Requirements and Commitments:

The review team has recommended two post-marketing requirements. These are related to transporters, and enumerated in the Approval letter.

Proprietary Name Risk Assessment:

The original, conditional, review by the Division of Medication Error Prevention and Analysis (DMEPA) determined that the proposed name, "Pradaxa," would not be particularly vulnerable to name confusion that could lead to medication errors. The name was not considered to be promotional in nature. However, their original review was based on the approval of two strengths of dabigatran: 110 and 150 mg. When the Division reached the conclusion that only the 150 mg strength should be marketed, DMEPA voiced a new concern.

The approval of only one strength of dabigatran would allow physicians to write prescriptions for Pradaxa without including the strength. There are currently two marketed drugs, Prenexa and Ridaura, that look and sound like "Pradaxa," and that are also available in only a single strength. Pradaxa could be confused with these drugs. Prenexa and Ridaura also overlap in many product characteristics.

Ultimately, however, the applicant agreed to market a 75-mg strength capsule for use in patients with renal insufficiency – estimated CrCL 15 to 30 mL/min. With the marketing of two strengths of Pradaxa, therefore, name confusion with Prenexa and Ridaura is a moot issue, because the prescriber will be required to write down the strength of Pradaxa in order to create a legally acceptable prescription. Thus, DMEPA finds the proposed proprietary name, "Pradaxa," acceptable for this product.

Advisory Committee:

This application was referred to the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on September 20, 2010. The Committee voted on the question: "Should dabigatran be approved for the reduction of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation?" The vote was "yes" = 9, "no" = 0, "abstain" = 0. There was considerable discussion about the advisability of approving only the 150 mg dose, vs. both the 150 and 110 mg doses (see "Two Doses or One?").

Conclusions:

For the reasons stated above, I am approving the NDA for dabigatran; however, the 110-mg strength will not be approved. A 75-mg strength will be approved for patients with renal dysfunction: CrCL 15 – 30 mL/min.

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/s/

ELLIS F UNGER
10/19/2010

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